

Use of brain natriuretic peptides (BNP), phosphorylated urodilatine, phosphorylated CDD/ANP and combinations thereof

5 The present invention relates to the use of the peptide hormones brain natriuretic peptides (BNP), phosphorylated urodilatine, phosphorylated CDD/ANP and combinations thereof for treating lung and/or bronchial disorders.

10 Obstructive lung diseases are characterized by spasm of bronchial muscles, a swelling of the bronchial mucosa and increased production of bronchial secretion in varying intensity. They include in particular bronchial asthma, chronic obstructive lung diseases (COLD) and also cardiac  
15 asthma. The administration of  $\beta_2$ -sympathomimetics (e.g. Fenoterol, Salbutamol, Terbutalen) is known for the therapy of obstructive lung diseases. The  $\beta_2$ -sympathomimetics lower the tone of the smooth bronchial muscles, they moreover inhibit release of mediator substances from mast cells and  
20 enhance the mucociliary clearance function. However, long-term and/or high-dose use of  $\beta_2$ -sympathomimetics may lead to desensitization of  $\beta_2$ -adenoreceptors and hence to a marked decrease in therapeutic efficacy.

25 The bronchodilatory action of urodilatine was established in both animal experiments (Flüge, Hoymann et al. Naunyn-Schmiedebergs Arch. Pharmacol. 345 Suppl. 2, 24 (1992)) and asthma patients (Flüge, Wagner et al. Naun. Schmied. Arch. Pharmacol. 345 Suppl. 2, 23; (1992)).

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Furthermore, the bronchodilatory activity of the atrial natriuretic peptide (ANP) in asthma is known (Hulks et al., Br. Med. J. 299 (1989), 1081-1982).

The object of the present invention was to provide a new therapeutic agent for lung and/or bronchial disorders, obstructive lung diseases in particular, which can be used  
5 instead of known therapeutic agents or in combination therewith and is superior to known agents such as, for example, the atrial natriuretic peptide and urodilatin in terms of the strength of the bronchodilatory action.

10 The object of the invention is accomplished by the provision of a pharmaceutical composition comprising brain natriuretic peptides (BNP), phosphorylated urodilatin, phosphorylated ANP and combinations thereof as active  
15 ingredient and optionally pharmaceutical conventional thinners, carriers, fillers or auxiliary substances for treating lung and/or bronchial disorders.

The pharmaceutical composition is particularly suitable for treating obstructive lung diseases.

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Administration of the composition is preferably parenteral, intravenous in particular (e.g. intravenous injections (as a bolus) or intravenous infusion), or by inhalation, with the dosage preferably amounting to 5 ng to 1000 µg of brain  
25 natriuretic peptides (BNP) per kg of body weight, more preferably 10 ng to 100 µg of brain natriuretic peptides (BNP) per kg of body weight. Administration in the abovementioned dosages via the intramuscular, subcutaneous, parenteral routes with protective medication is also  
30 suitable.

It has been demonstrated in animal experiments that parenteral administration of brain natriuretic peptides

(BNP), phosphorylated urodilatine, phosphorylated ANP and combinations thereof leads to significant protection, which manifests itself in improved forced expiration in particular, in bronchoconstriction induced by inhalation of acetylcholine.

It has surprisingly been found here that the action of brain natriuretic peptides (BNP), phosphorylated urodilatine, phosphorylated ANP and combinations thereof in the same dose range was markedly superior to the atrial natriuretic peptide (ANP) and urodilatine.

The invention is further clarified by the following example.

#### Example

The bronchodilatory action of brain natriuretic peptides (BNP) was demonstrated in adult albino guinea pigs based on the method of Hutson et al. (Am. Rev. Respir. Dis. 137, 548; 1988) using the enhanced experimental design of Bent, Eltester, Forsting and Schmitz (Naunyn-Schmiedbergs Arch. Pharmacol. Suppl. 1, 381; (1992)). Here, conscious animals are sat in an bodyplethysmograph in which the degree of bronchoconstriction was measured by means of respiratory pressure and the maximum of the inspiratory flow-volume curve. Respiratory rate and respiratory volume were also measured. The animals were exposed to an aerosol of a 0.3% strength histamine solution in the air for 30 s to achieve optimal bronchoconstriction. Each animal served as its own control in preliminary experiments determining the degree of histamine provocation.

In the conscious guinea pigs, an intraperitoneally injected dose of 320 ng of brain natriuretic peptides (BNP)/kg of body weight achieved a pronounced bronchodilatory effect which was clearly superior in terms of potency to urodilatin in the same dosage. The atrial natriuretic peptide was found in these experiments on 18 animals to have an even lower bronchodilatory effect than urodilatin. The brain natriuretic peptide was thus superior in potency to the two peptides already described to have bronchodilatory action.

CLAIMS

1. The use of a pharmaceutical composition comprising  
5 brain natriuretic peptides (BNP), phosphorylated  
urodilatine (P-uro), phosphorylated ANP (P-CDD/ANP)  
and combinations thereof as active ingredient and  
optionally pharmaceutically conventional thinners,  
carriers, fillers or auxiliary substances for treating  
lung and/or bronchial disorders.
- 10 2. The use as claimed in claim 1 for treating obstructive  
lung diseases.
- 15 3. The use as claimed in claim 1 or 2, characterized in  
that the composition is administered parenterally,  
parenterally with protective medication,  
intramuscularly, subcutaneously, as aerosol, by  
intravenous infusion or as an intravenous bolus, and  
by inhalation.
- 20 4. The use as claimed in any of claims 1 to 3,  
characterized in that the composition comprising any  
of the active ingredients mentioned in claim 1 or  
combinations thereof is administered in a dosage of  
25 5 ng to 1000 µg per kilogram of body weight.
- 30 5. The use as claimed in claim 4, characterized in that  
the composition comprising any of the active  
ingredients mentioned in claim 1 or combinations  
thereof is administered in a dosage of 10 ng to 100 µg  
per kilogram of body weight.

6. The use of a pharmaceutical composition comprising any of the active ingredients mentioned in claim 1 or combinations thereof and optionally pharmaceutically conventional thinners, carriers, fillers or auxiliary substances for the preparation of a medicament for treating lung and/or bronchial disorders.
7. The use as claimed in claim 6 for the preparation of a medicament for treating obstructive lung diseases.
8. The use as claimed in claim 6 or 7, characterized in that a medicament which can be administered parenterally intravenously or by inhalation is prepared.
9. The use as claimed in any of claims 6 to 8, characterized in that a dosage unit of the medicament of 5 ng to 1000 µg of any of the active ingredients mentioned in claim 1 or any combination of the active ingredients per kilogram of body weight is administered.
10. The use as claimed in claim 9, characterized in that a dosage unit of the medicament of 10 ng to 100 µg of any of the active ingredients mentioned in claim 1 or any combination of the active ingredients per kilogram of body weight is administered.
11. A method for treating lung and/or bronchial disorders, characterized in that a pharmaceutical composition comprising any of the active ingredients mentioned in claim 1 or combinations thereof and optionally

pharmaceutically conventional thinners, carriers, fillers or auxiliary substances is administered.

5 12. The method as claimed in claim 11 for treating obstructive lung diseases.

13. The method as claimed in claim 10 or 11, characterized in that the composition is administered parenterally intravenously or by inhalation.

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14. The method as claimed in any of claims 10 to 13, characterized in that the composition is administered in a dosage of 5 ng to 1000 µg per kilogram of body weight which comprises any of the active ingredients mentioned in claim 1 or combinations thereof.

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15. The method as claimed in any of claims 10 to 14, characterized in that the composition is administered in a dosage of 10 ng to 100 µg per kilogram of body weight which comprises any of the active ingredients mentioned in claim 1 or combinations thereof.

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